Remarks

Claims 1, 2, 7-63, and 65-79 are pending in the application. Claims 25, 28, 34-36, and 41-44 have been withdrawn from consideration by the Examiner. Claims 1, 2, 7-24, 26, 27, 29-33, 37-40, and 45-79 stand rejected. Claims 1, 2, 63, 65, 69, and 73 have been amended, and claims 49, 50, 52, 55, and 56 have been canceled. Support for the amendments to claims 1, 2, 65, 69, and 73 is found in the specification on page 17, lines 1-2; page 18, lines 7-8; page 25, lines 10-12; and original claim 56 . Applicant respectfully requests reexamination and reconsideration of the case in light of the following remarks. Each of the rejections levied in the Office Action is addressed individually below.

I. **Rejection under 35 U.S.C. § 112, first paragraph (new matter).** Claims 1, 2, 7-24, 26, 27, 29, 30-33, 37-40, 45-62, and 65-78 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicant submits that this rejection is rendered moot by the present Amendment.

II. **Rejection under 35 U.S.C. § 112, second paragraph, as being indefinite.** Claims 1, 2, 7-24, 26, 27, 29, 30-33, 27-40, 45-62, and 65-78 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner maintains that the word "substantially" in base claims 1, 2, 65, 69, and 73 is indefinite. Applicant submits that the present Amendment renders this rejection moot.

III. **Rejection under 35 U.S.C. § 102(b) or § 103, in view of Sutton *et al.*, U.S. Patent 6,204,054.** Claims 1, 2, 7-17, 20-24, 26, 27, 29-33, 37-38, 40, 45-47, 49-62, 65-70, 73-74, and 77-79 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Sutton *et al.* (U.S. Patent 6,204,054), or under § 103 as being unpatentable over Sutton *et al.* (U.S. Patent 6,204,054). The Examiner states that Sutton teaches the making of a matrix or microparticle composed of at least three components selected from a lipid, a protein, a sugar, and a polymer. And, therefore, the

Examiner concludes that Sutton anticipates or renders obvious the claimed invention in the present application. The Examiner's reading of Sutton is incorrect. Sutton does not anticipate or render obvious the claimed invention.

The claims of the present application recite microparticles with a lipid-protein-sugar matrix or a matrix with at least three components selected from the group consisting of lipids, proteins, sugars, and synthetic polymers. The claimed microparticles include at least three components in the matrix of the microparticles. Sutton does not teach this aspect of the invention. Sutton does not teach microparticles with three matrix components such as a lipid, a protein, and a sugar.

Sutton teaches the use of transcytosis vehicles and enhancers to deliver physiologically-active agents. Transcytosis vehicles and enhancers, as Sutton recites, include albumin, anti-GP60 antibodies, GP60 peptide fragments, protein disulphide isomerase (PDI), and fragments thereof. See column 2, lines 46-51, of U.S. Patent 6,204,054. Starting at column 7, lines 56, Sutton describes mixing the transcytosis enhancer or vehicle with a variety of other materials. The listed materials include sugars, polymers, and emulsifiers. The long list of possible materials for including with the transcytosis vehicles and enhancers in a microparticle does not constitute teaching one of skill in the art how to make lipid-protein-sugar microparticles or other particles with at least three components selected from the group consisting of lipids, proteins, sugars, and synthetic polymers. Sutton does not teach anywhere the use of at least three components in the matrix of the microparticles. In contrast, Applicant specifically teaches and claims microparticles with at least three matrix components. Without a teaching of this aspect of the invention, Sutton cannot anticipate or render obvious the claimed invention.

Furthermore, solely to further prosecution, Applicant has amended base claims 1, 2, 63, 65, 69, and 73 to recite specific ranges for each of the components lipid, protein, and sugar. The matrix of the recited particles contains 3-99% by weight lipid, 1-60% by weight protein, and 0.5-50% by weight sugar. Sutton does not teach these ranges for the individual components and certainly does not teach these three ranges combined. Applicant, therefore, requests that the rejection be removed.

In addition, Sutton does not teach the aspects of the claims recited in dependent claims 38 (wherein the sugar is lactose), 49 (wherein the lipid comprises 0-99% of the matrix by weight),

51 (wherein the lipid comprises 20-60% of the matrix by weight), 53 (wherein the protein comprises 10-30% of the matrix by weight), 57 (wherein the sugar comprises 10-30% of the matrix by weight), and 79 (matrix comprising dipalmitoylphosphatidylcholine (DPPC), lactose, and albumin). Since Sutton does not specifically teach the limitations in these dependent claims, Sutton cannot anticipate these claims. Applicant, therefore, requests that the rejection of these claims be removed.

IV. **Rejection under 35 U.S.C. § 103 as being unpatentable over Sutton *et al.* (U.S. Patent 6,204,054) taken with Grinstaff *et al.* (U.S. Patent 5,639,473).** Claims 1, 18, 19, and 73-76 stand rejected under 35 U.S.C. § 103 as being unpatentable over Sutton *et al.* (U.S. Patent 6,204,054) in view of Grinstaff *et al.* (U.S. Patent 5,639,473). The Examiner cites Grinstaff *et al.* for the teaching that it is well established in the prior art that DNA immunogenic compositions can be used in combination with a polymeric or particle based carrier for enhancing the controlled release and bioavailability of an expressed antigen *in vivo*. Even if Grinstaff teaches the combination of DNA plus a polymeric or particle-based carrier, Grinstaff does not teach particles with a lipid-protein-sugar matrix. Neither of these references teaches this aspect of the invention. The references merely include an exhaustive list of many different excipients, polymers, emulsifiers, sugars, *etc.*, which might be included in the microparticles. Such a teaching is not novelty destroying, and such a teaching does not render the claimed invention obvious. Furthermore, Applicant has amended base claims 1 and 73 to recite specific ranges for the lipid, protein, and sugar in the matrix. Neither Sutton, as discussed above, nor Grinstaff teaches these ranges for the individual matrix components. And certainly neither teaches these three ranges combined. The Examiner must point out an explicit teaching of all aspects of the claimed invention, including the specified ranges of each component, in order to establish a *prima facie* case of obviousness. Since the references, even when combined, do not teach all aspects of the invention, the Applicant respectfully requests that the rejection be removed.

V. **Rejection under 35 U.S.C. § 103 as being unpatentable over Sutton *et al.* (U.S. Patent 6,205,054) taken with Wheeler *et al.* (U.S. Patent 5,976,567).** Claims 69, 71, and 72

stand rejected under 35 U.S.C. § 103 as being unpatentable over Sutton *et al.* (U.S. Patent 6,205,054) taken with Wheeler *et al.* (U.S. Patent 5,976,567). The Examiner admits that Sutton does not teach that the transcytosis enhancers and vehicles and microparticles thereof can be used to deliver a DNA coding for a protein and that they can be used to transfect hematopoietic or embryonic stem cells. Examiner cites Wheeler for the use of lipid (DPPC)-based carriers in the transfection of stem cells. However, as discussed above, even the combination of these two references does not lead to the recited lipid-protein-sugar particles in base claim 69. Without a teaching for these particles with the particular ranges for each component, the combination of Sutton and Wheeler cannot render obvious the claimed invention because not all aspects of the claims have been taught by Sutton and Wheeler. Applicant, therefore, requests that the rejection be removed.

VI. Rejection under 35 U.S.C. § 103 as being unpatentable over Hanes *et al.* (U.S. Patent 5,855,913). Claims 1, 2, 7-24, 26, 27, 29-31, 33, 37-40, 45-63, 65-69, and 73-78 stand rejected under 35 U.S.C. § 103 as being unpatentable over Hanes *et al.* (U.S. Patent 5,855,913). The Examiner maintains that Hanes *et al.* teach "a polymeric microparticle of less than 10 μm in diameter for use as a controlled release-encapsulated carrier of biologically active molecules such as DNA or DNA coding for a gene of interest, wherein the microparticles are composed of a combination of biocompatible materials selected from DPPC, copolymers, protein excipients (any known polymeric polypeptide or copolymers thereof) and a sugar (lactose)." Applicant disagrees with the Examiner's assessment of Hanes.

Hanes teaches particles incorporating a surfactant for drug delivery to the pulmonary system. Hanes states that the surfactant may be incorporated throughout the particle or may be coated on the particle's surface. The reference also lists many exemplary surfactants for use in the particles. The surfactant improves various surface properties of the particles including reducing particle-particle interactions. Hanes describes the particles as being formed from biocompatible polymers such as polyanhydrides, polycarbonates, polyalkenes, and other synthetic polymers; celluloses; polysaccharides; peptides; and proteins. Particles formed from only surfactant and the agent to be delivered are also described. Hanes does *not* teach or suggest the particular combinations of materials recited in the claims. Furthermore, Hanes does *not* teach

the particular ranges for the lipid, protein, and sugar found in the matrix of the claimed particles. The contribution of Hanes to the art is the use of surfactants in particles for drug delivery to the pulmonary system and not the use of a particular combination of components (*e.g.*, 3-99% lipid, 1-60% protein, and 0.5-50% sugar) to form the matrix of microparticles.

Although Hanes may mention each of the materials recited in the claims as Sutton does, Hanes does not teach the use of the particular triple combinations of these materials in the matrix of a particle within the recited ranges. The claimed invention recites the use of a particular combination of three components selected from proteins, lipids, sugars, and synthetic polymers in the inventive microparticles. Hanes does not teach that any triple combination of biocompatible materials can be used to make the matrix of the particles as the Examiner has suggested. In fact, Hanes does not prepare any microparticles with the combinations of materials as claimed in the present invention. For example, the examples in Hanes describe particles made with poly[(p-carboxyphenoxy)-hexane anhydride], particles made with poly(D,L-lactic-co-glycolic acid) (PLGA 50:50), particles made with the protein lysozyme, particles made with dextran-DEAE, particles made with trehalose, and particles made with polyethylene glycol. Hanes does mention that these particles may be formed with a surfactant such as DPPC. The resulting particles only have *two* components in the matrix—lipid plus the other material. Hanes does not describe the use of three components in the matrix of the particles as claimed in the present invention.

Hanes only describes the use of at most two components—a lipid; and a synthetic polymer, protein, or sugar. Since Hanes does not teach or even suggest a combination of three components in the recited ranges, Hanes cannot anticipate or render obvious the claimed invention. Applicant requests that the rejection be removed.

VII. Rejection under 35 U.S.C. § 103(a), as being unpatentable over Hanes *et al.*, U.S. Patent 5,855,913, taken with any of Grinstaff, Sutton, Rypacek, and further in view of Wheeler. Claims 1, 2, 7-24, 26, 27, 29-33, 37-40, 45-69, and 73-79 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hanes *et al.* taken with any of Grinstaff *et al.*, Sutton *et al.*, or Rypacek *et al.*, and further in view of Wheeler *et al.* The Examiner states that Hanes *et al.* do not claim explicitly minor modification such as known DNAs, RNAs, or plasmids

encoding for an antigen, ratios of agents being used in the formulations, and/or a particular combination of known matrix polymers (albumin and/or other known polymer), lipids and excipient(s) such as any other sugar (cellulose). The Examiner continues that such modifications would have been obvious to one of ordinary skill in the art as minor modifications that can be practiced as a matter of design choice by a person of ordinary kill in the art of polymers, particularly in view of the totality of the prior art of record as set forth in Grinstaff *et al.*, Sutton *et al.*, or Rypacek *et al.* Applicant disagrees.

In response to the Applicant's argument in the last Response that Hanes does not teach or suggest the particular combinations of materials recited in the claim, the Examiner states that "there clearly exists general art accepted motivations for formulating an excipient such as a sugar into the DPPC/protein/polymer blends of Hanes." However, Hanes does not teach a DPPC/protein/polymer blend. Hanes at most teach two components in the matrix of the particles—a lipid and another material. Plus, there is no motivation from any of the references to include sugar in the particles of Hanes. Applicant respectfully submits that the Examiner is using hindsight to piece together the various components of the matrix. This is not allowed. The teaching or suggestion to combine must come from the references themselves or from general knowledge in the art. The Examiner has cited no reason to include sugar, for example, in the particles taught by Hanes.

As pointed out above, Hanes *et al.* fails to teach a combination of three components selected from proteins, sugars, lipids, and synthetic polymers. The other references cited also fail to teach such a combination of at least three components in the matrix of the microparticles. Therefore, even when all five references are combined, the combination fails to teach or suggest such a combination.

Furthermore, the combined references do not teach the ranges of the components of the matrix recited in the base claims. Therefore, the combination of references cannot render obvious the claimed invention, and Applicant requests that the rejection be removed.

In view of the forgoing amendments and arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

C. Hunter Baker, M.D., Ph.D.
Registration Number: 46,533

Choate, Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109
(617) 248-5000
Date: June 13, 2005

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